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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,400	03/30/2001	Yehuda Shoenfeld	01/21885	1174

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EXAMINER	
SCHWADRON, RONALD B	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,400	SHOENFELD ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,19 and 26-28* is/are pending in the application.

4a) Of the above claim(s) *26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,19,27,28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

1. Applicant's election with traverse of the species IL-10 in the reply filed on 6/10/2004 is acknowledged. The traversal is on the ground(s) that are stated. This is not found persuasive because the art recognizes that IL-10 and TGFB are different cytokines with different amino acid sequences and different structural and functional properties.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicant's election of ox ldl in the reply filed on 2/1/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claim 26 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/1/2005..

4. Claims 14,19,27,28 are under consideration.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The rejection of claims 14,18-20,26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons elaborated in paragraph 9 of the Office Action mailed 6/24/2003 is withdrawn in view of the amended claims and cancellation of claims 18 and 20.

7. Claims 14,19,27,28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "administration is in a sufficient amount to induce production of IL-10 or TGFβ and to suppress IFN-γ " in claims 14,27 and 28. Regarding applicants comments about page 3 of the specification, the particular passage to which applicant refers does not disclose the claimed method with the aformentioned limitation. It discloses a summary of the prior art. The specification page 13, lines 16-19 does not disclose a method with the aforementioned limitation. It refers to a *possible* mechanism of action (are possibly mediated via a stimulation and production of cytokine TGFB and the development of nonspecific suppresser T-cells) which does not even disclose the particular limitation under consideration. Regarding applicants comments about the specification, pages 18 and 20, said passage discloses that assays for IL-4, IL-10, IFN-y, and TGFB are to be performed, but no results from said assays are provided. There is no support for the scope of the claimed invention in the specification as originally filed (the claimed invention constitutes new matter).

8. Claims 14,19,27,28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

The specification is not enabling for the claimed method of preventing or treating atherosclerosis using an oral tolerance inducing dosage of modified ldl or ox ldl. The specification does not disclose how to use the claimed method in vivo in humans to treat or prevent disease. Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification because the use for the instant invention disclosed in the specification is the treatment or prevention of disease in humans. The state of the art is such that is unpredictable in the absence of appropriate evidence as

to how the instant invention could be used for preventing or treating atherosclerosis using an oral tolerance inducing dosage of modified LDL or OxLDL.

Judge Lourie stated in Enzo Biochem Inc. v. Calgene Inc. CAFC 52 USPQ2d 1129 that:

The statutory basis for the enablement requirement is found in Section 112, Para. 1, which provides in relevant part that:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. . . .

35 U.S.C. Section 112, Para. 1 (1994). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " Genentech, Inc. v. Novo Nordisk, A/S , 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright , 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see Hybritech, Inc. v. Monoclonal Antibodies, Inc. , 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), which in this case is October 20, 1983 for both the '931 and '149 patents. 8

We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, e.g., Wands , 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In In re Wands , we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows:

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.
Id. at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See Amgen, Inc. v. Chugai Pharm. Co., Ltd. , 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the Wands factors "are illustrative, not mandatory. What is relevant depends on the facts.").

Regarding Wands factors (4) and (8), the claims encompass treatment or prevention of atherosclerosis in vivo in humans. Regarding Wands factors (5) and (7), there is a high degree of unpredictability in the art. For example, Spack teaches that attempts to treat MS via inducing oral tolerance to myelin protein have been unsuccessful (see abstract). Similarly, the art recognizes that attempts to treat rheumatoid arthritis via inducing oral tolerance to collagen have been unsuccessful (see McKown et al.). Thus, it is recognized in the art that it is unpredictable whether human disease can be treated via inducing oral tolerance to a disease antigen. Regarding Wands factor (3), while the specification provides an example in a mouse model, there were copious amounts of mouse research that suggested that oral tolerance could be used to treat MS or rheumatoid arthritis, yet said diseases were not successfully treated in humans using oral tolerance. Regarding Wands factor (2), there is no disclosure in the specification as to what doses would be used to induce the functional parameters recited in the claim which are related to properties of the oral tolerance induction mechanism.
Based on the aforementioned undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification.

Regarding applicants comments, applicant has not addressed the Spack and Mckown references. Spack teaches that attempts to treat MS via inducing oral tolerance to myelin protein have been unsuccessful (see abstract). Similarly, the art recognizes that attempts to treat rheumatoid arthritis via inducing oral tolerance to collagen have been unsuccessful (see McKown et al.). Thus, it is recognized in the art that it is unpredictable whether human disease can be treated via inducing oral tolerance to a disease antigen. Regarding Wands factor (3), while the specification provides an example in a mouse model, there were copious amounts of mouse research that

suggested that oral tolerance could be used to treat MS or rheumatoid arthritis, yet said diseases were not successfully treated in humans using oral tolerance. Regarding Wands factor (2), there is no disclosure in the specification as to what doses would be used to induce the functional parameters recited in the claim which are related to properties of the oral tolerance induction mechanism. Regarding applicants comments, pages 19 of the specification refers to doses given to mice in a prophetic experiment for which no results were provided. Thus, it is unclear as to whether a particular dosage actually had any effect. The specification, page 18 refers to a single dosage given to mice. There is no disclosure in the specification as to dosages to be used in humans or what doses would be used to induce the functional parameters recited in the claim which are related to properties of the oral tolerance induction mechanism. Regarding the use of modified ldl in the claimed method, Yesair et al. teach a composition for oral administration containing LPC (see column 5, last paragraph and Examples). LPC is also a derivative of ox ldl (see specification, page 5, first complete paragraph). LPC is a modified LDL. The specification discloses that LPC has the properties of ox ldl. The specification, page 11, fourth paragraph *discloses that LPC can be used in the claimed method.* Yet the Harats declaration discloses that LPC and other forms of modified LDL cannot be used in the claimed method (see sections 7-9). Thus, the specification does not provide guidance as to what forms of modified LDL can be used in the claimed method. In addition, the specification discloses that:

"Lysophosphatidylcholine (LPC) is expressed in human atherosclerotic plaques. It is an active biological substance that can induce the first steps of atherogenesis. Indeed it is even more potent than Ox LDL."(see page 5, penultimate paragraph).

Thus, even though LPC is involved in the pathogenesis of atherogenesis, oral tolerance to LPC cannot be used to treat atherosclerosis.

Regarding the Harats declaration and the LDLR mice model, Wouters et al. discloses that the LDLR mouse displays cholesterol metabolic pathways not found in humans (see page 474, second column, second paragraph)) and as a consequence "This route can serve as a backup mechanism for lipoprotein clearance in ldlr mice, yielding unforeseen side effects "(page 474, second column, first paragraph). Applicant has referred to a variety of publications that were not furnished and are not of record. Applicants comments regarding said publications have not been considered.

9. Claims 27 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Yesair et al. (US Patent 4,874,7695) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Yesair et al. teach a composition for oral administration containing LPC (see column 5, last paragraph and Examples). LPC is also a derivative of Ox LDL (see specification, page 5, first complete paragraph). LPC is a modified LDL. The pharmaceutically acceptable carrier is the other lipids contained in the composition taught by Yesair et al. (see column 5). Yesair et al. teach the in vivo administration of said composition (see Examples and column 13, last paragraph). It is an inherent property that administration of the claimed composition results in the method of claim 14, because the method taught by Yesair et al. involves administration of the same compound (LPC) to the same population (eg. any individual, because it would be desirable to prevent atherosclerosis in any individual). Regarding the functional properties as pertaining to the dosage recited in claim 14, there is no disclosure in the specification as to a particular range or concentration of the administered agent that would result in the functional activities. Therefore it will be assumed for the purposes of prior art that the dose is not relevant or critical to said properties.

Regarding the Harats declaration, the specification, page 11, fourth paragraph discloses that LPC can be used in the claimed method. Applicant needs to explain why the specification discloses that LPC can be used to treat atherosclerosis whilst the Harats declaration discloses that it cannot be used to treat atherosclerosis. It is unclear as to whether these two different results are the result of differences in experimental protocol. Regarding the presence of "other lipids" in the preparation disclosed by Yessair et al., the claimed methods "comprising" encompasses use of additional ingredients in addition to the modified LDL.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 14,19,27,28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sima et al. (11th Int. Symp. on Atherosclerosis, page 227, October 1997) and Hansson et al. (11th Int. Symp. on Atherosclerosis, page 289, October 1997)in view of Punnonen et al. (US Patent 6,541,011).

Sima et al. teach that ox ldl is an immunoreactive component in the atherosclerotic process in humans with atherosclerosis and a hamster model of atherosclerosis (see entire abstract, especially last sentence). Sima do not disclose treatment with an oral tolerance inducing amount of ox ldl. Hanson et al. disclose that T cell reactivity against ox ldl contributes to atherosclerosis (see abstract). Punnonen et al. teach that oral tolerance has been used in a variety of mouse models to induce tolerance to autoantigens (column 27, third paragraph). The orally administered antigen is administered with a carrier suitable for oral administration. The induction of oral tolerance can be used to establish whether the disease induced in the aforementioned hamster model is immunologically mediated. It could also potentially reveal what immune mechanisms are involved in the aforementioned model (eg. antibody versus T cell, etc). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Sima et al. disclose an animal model of atherosclerosis wherein ox ldl is an immunoreactive component in the atherosclerotic process and Hanson et al. disclose that T cell reactivity against ox ldl contributes to atherosclerosis whilst Punnonen et al. teach that oral tolerance has been used in a variety of mouse models to induce tolerance to autoantigens. One of ordinary skill in the art would have been motivated to do the aforementioned to determine if the hamster model of Sima et al. could be treated using

oral tolerance. The functional parameters recited in the claim regarding cytokine secretion are mechanisms of action that would presumably occur in oral tolerance if they actually are pertinent to the oral tolerance mechanism.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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